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Magnetic resonance imaging and positron emission tomography findings in status epilepticus following severe hypoglycemia

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We recently experienced a case with asymmetrical cortical abnormality on MRI with focal status epilepticus following severe hypoglycemia. The cerebral blood flow and metabolisms for oxygen and glucose were determined using positron emission tomography (PET) during focal status epilepticus following severe hypoglycemia and at the follow-up period. Prolonged seizure activity produced profound glucose hypermetabolism and mild hyperemia in the region of the presumed cortical focus of epilepsy and in structures anatomically remote from the focus, corresponding to the areas of abnormal signal intensity on the MRI. The patient remained comatose and exhibited a diffuse hypoperfusion/ hypometabolism and symmetrical brain atrophy on the follow-up PET and MRI, respectively. Cytotoxic brain edema due to profound glucose metabolism without compensatory increase of the blood flow during status epilepticus may account for the brain abnormality observed on the early MRI. Simultaneous examination of the cerebral blood flow and metabolism using PET can provide useful information about the pathology in patients with status epilepticus.

Key words: cerebral blood flow, hypoglycemia, glucose metabolism, positron emission tomography (PET), status epilepticus

INTRODUCTION

HYPOGLYCEMIA, even when severe and leading to coma, does not usually result in permanent neurological damage.[1–3] However, prolonged seizure activity following profound hypoglycemia may increase the risk of irreversible neurological damage because of poor energy supply in the face of the markedly elevated demand brought on by the seizures.[4] Symmetrical brain damage is usually demonstrated neuroradiologically in the brain after hypoglycemic coma.[5] We describe a case with asymmetrical brain abnormality on magnetic resonance imaging (MRI) with focal status epilepticus following severe hypoglycemia. Profound glucose hypometabolism and mild hyperemia were observed during focal status epilepticus on the positron emission tomography (PET) images, corresponding to the areas of abnormal signal intensity on the MRI. The patient remained comatose and exhibited a diffuse hypoperfusion/hypometabolism in the brain and resulted in a symmetrical severe brain atrophy on the follow-up PET and MRI, respectively. The possible pathogenesis of asymmetrical signal abnormality on the initial MRI and symmetrical brain atrophy on the follow-up MRI is discussed.

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PET MEASUREMENT

FDG-PET scanning

Enteral and parenteral sources of glucose were withheld for 6 hours before the PET examination. Before tracer injection, a 5-minute transmission scan using a ^{68}Ge rod source was obtained to correct tissue attenuation. A 60-minute dynamic PET scan (40 s × 1; 20 s × 2; 40 s × 4; 60 s × 4; 180 s × 4; 300 s × 8) was performed using an EXACT HR+ PET scanner (Siemens) after an intravenous injection of [^{18}F]-2-fluorodeoxyglucose ([^{18}F]-FDG) at a dose

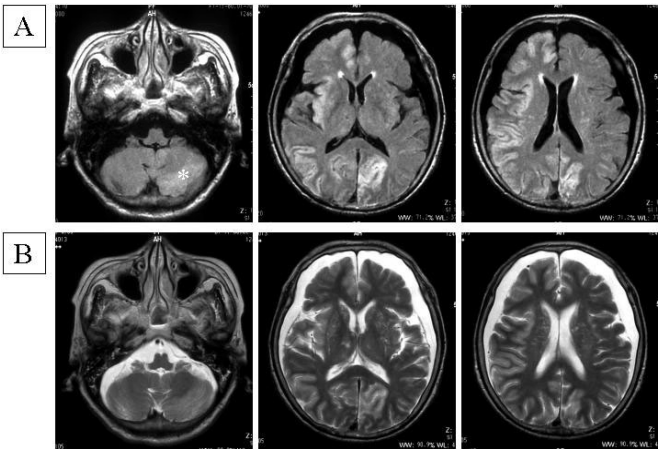
of 3.0–4.0 MBq/kg. Emission data corrected for random, dead time, and attenuation were reconstructed with filtered back-projection. Arterial blood samples were withdrawn from the brachial artery at 15-second intervals for the first 3 min, followed by increasingly longer intervals to 60 min, to measure arterial plasma radioactivity using an auto well gamma counter (ARC-400, Aloka, Tokyo, Japan). The blood sample obtained at 30 min after the injection was analyzed for blood glucose concentration. Five parameters (K_1, k_2, k_3, k_4, and blood volume) were estimated by use of the nonlinear least-square fitting technique. As an index of the glucose cerebral metabolic rate (CMR_{glc}), the FDG uptake constant (K_i) was calculated as $K_1*[k_3/(k_2+k_3)]$. With lumped constant (LC) for normal brain and the arterial plasma glucose concentration (Ca_{glc}), absolute values for CMR_{glc} were related to K_i as $(Ca_{glc}*K_i)/LC$.

^{15}O gas-PET scanning

Before emission scanning, a 5-minute transmission scan using a ^{68}Ge rod source was obtained to correct tissue attenuation. Intermittent arterial blood sampling and radioactivity measurements were performed throughout PET scanning using a catheter implanted in the brachial artery to obtain the arterial input function. One-minute inhalation of $C^{15}O$ (2 GB/min) followed by a 3-minute static scanning and 3 blood samplings were obtained to measure the cerebral blood volume. The $C^{15}O_2$ slow bolus inhalation method was used to measure the cerebral blood flow (CBF). A 10-minute dynamic scanning (30 s × 1; 15 s × 10; 30 s × 10; 60 s × 2) was performed following 2 min of slow bolus inhalation of $C^{15}O_2$ gas (1.5 GB/min). The arterial input function was determined by frequent arterial blood sampling. Finally, after a 7-minute inhalation of $^{15}O_2$ (0.5 GB/min), a steady-state O_2 image was scanned and 3 arterial blood samplings were obtained for 5 min to determine the oxygen extraction fraction (OEF) and the cerebral metabolic rate for oxygen ($CMRO_2$).

CASE REPORT

A 79-year-old female with a long history of insulin-dependent diabetes mellitus was admitted in a coma, having been found in confusion a few hours earlier by her spouse. On admission, her hemodynamics and respiration were stable but she was unresponsive with a Glasgow coma score of 5/15. She had intermittent left-sided clonic seizures initiating from the face. Serum glucose was found to be less than 30 mg/d*l*. The patient was immediately given an intravenous bolus of 40 m*l* of 10% glucose solution followed by continuous administration of 5% glucose solution. Emergency computed tomography (CT) scan of her brain showed no abnormality except for an old lacunar infarction in the right thalamus. Her blood glucose level was normalized without an improvement of consciousness. Follow-up brain CT scan on the next day was also unremarkable. She had prolonged left-sided clonic seizures with infrequent secondary generalization in spite of aggressive treatment with anticonvulsants. MRI study was performed on the 5th hospital day (Fig. 1). The fluid-attenuated inversion recovery (FLAIR) (Fig. 1A) and T_2-weighted (Fig. 1B) axial images demonstrated an extensive area of increased signal intensity involving the right cerebral cortex including insular regions and the left occipital cortex. Increased signal intensity was also obvious in the left cerebellar cortex on the FLAIR image. The cerebral metabolic rate for glucose (CMR_{glc}) was determined after an intravenous injection of 148 MBq of [^{18}F]-FDG on the 4th hospital day (Fig. 2A). Increased glucose metabolism ($rCMR_{glc}$: 72–77 μmol/100 g/min) was observed in the right frontal, parietal, and occipital cortices, corresponding to the areas of abnormal signal intensity on the MRI. This value was apparently higher than that observed in the normal cortex ($rCMR_{glc}$: 44.3 ± 6.0 μmol/100 g/min) in 14 controls (mean age 56.5 ± 14.7 years). The right temporal cortex showed increased signal intensity on the FLAIR image, but exhibited normal glucose metabolism ($rCMR_{glc}$: 47 μmol/100 g/min). Glucose hypermetabolism was also observed in the right thalamus ($rCMR_{glc}$: 73 μmol/100 g/min) and the left cerebellar cortex ($rCMR_{glc}$: 72 μmol/100 g/min). The left cerebral hemisphere exhibited normal glucose metabolism ($rCMR_{glc}$: 41–44 μmol/100 g/min) except for the occipital cortex which showed slightly increased glucose metabolism ($rCMR_{glc}$: 49 μmol/100 g/min). The cerebral blood flow (CBF), cerebral blood volume (CBV), cerebral metabolic rate for oxygen ($CMRO_2$), and oxygen extraction fraction (OEF) were determined on the 5th hospital day (Fig. 2B). Mild hyperemia was observed in the right cerebrum and the regional CBF in the right cerebral cortex (rCBF: 51–55 m*l*/100 g/min) was higher compared with that in the left cerebral cortex (rCBF: 43–49 m*l*/100 g/min) (Fig. 2B). The value observed in the left cerebral cortex was slightly higher than that observed in the normal cortex (rCBF: 45.6 ±1.3 m*l*/100 g/min) in 10 controls (mean age 61.2 ± 13.0 years). Mild hyperemia was also observed in the left cerebellar hemisphere and vermis (Fig. 2B). Interestingly, the regional $CMRO_2$ was not different between the two hemispheres ($rCMRO_2$: right 2.3–3.0 m*l*/100 g/min, left 2.6–2.9 m*l*/100 g/min) except for the left occipital cortex which exhibited low oxygen metabolism ($rCMRO_2$: 1.6 m*l*/100 g/min) (Fig. 2B). These values observed in the cerebral cortices were almost the same as that observed in the normal cortex ($rCMRO_2$: 2.9 ± 0.3 m*l*/100 g/min) in 10 controls. An EEG recording from the scalp demonstrated excessive θ waves with multifocal frequent spike discharges on the 6th hospital day. Although the convulsion ceased within one week, the patient remained in a coma. Follow-up MRI examined on the 33rd hospital day showed severe symmetrical brain atrophy especially in the frontal and temporal lobes (Fig. 3). The areas of increased signal intensity



◀ **Fig. 1** The magnetic resonance image on the 5th day after hypoglycemic coma. The axial fluid-attenuated inversion recovery (FLAIR) (A) and T_2-weighted (B) images during focal status epilepticus demonstrated increased signal intensity in the right cerebral cortex including insular regions and the left occipital cortex. Increased signal intensity was also seen in the left cerebellar cortex (∗).

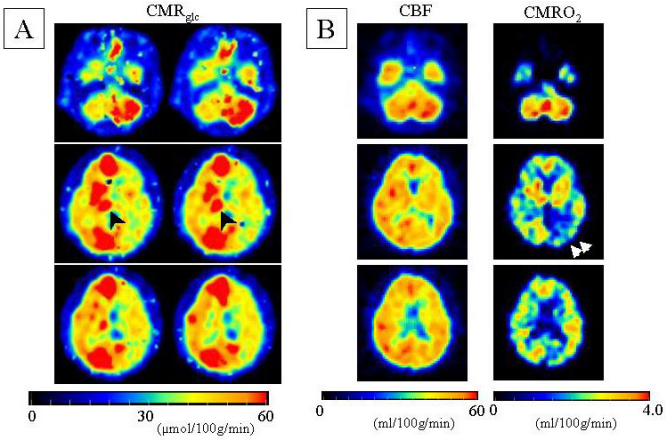
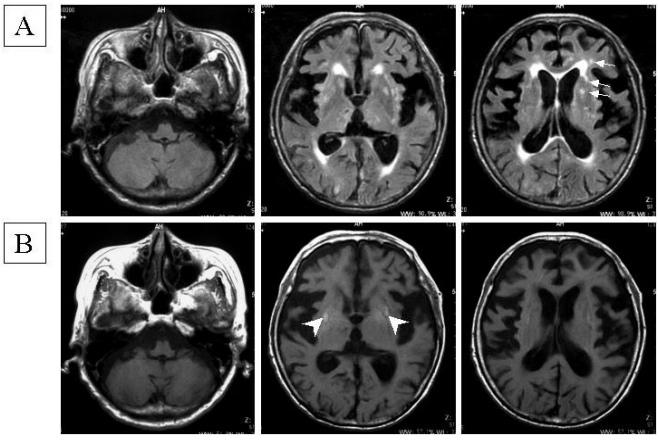


Fig. 2 The cerebral metabolic rate for glucose (CMR_{glc}) ▶ evaluation with FDG-PET on the 4th day after hypoglycemic coma (A). The cerebral blood flow (CBF) and cerebral metabolic rate for oxygen ($CMRO_2$) evaluations with PET on the 5th day after hypoglycemic coma (B). (A) Increased glucose metabolism was observed in the right frontal, parietal, and occipital cortices, corresponding to the areas of abnormal signal intensity on the MRI. Glucose hypermetabolism was also observed in the right thalamus (*black arrowhead*) and the left cerebellar cortex. (B) Mild hyperemia was observed in the right cerebrum especially in the insular region and the left cerebellar hemisphere and vermis. Regional $CMRO_2$ was not different between the two hemispheres except for the left occipital cortex which exhibited low oxygen metabolism (*double arrow*).



◀ **Fig. 3** The magnetic resonance image on the 33rd day after hypoglycemic coma. The axial fluid-attenuated inversion recovery (FLAIR) (A) and T_1-weighted (B) images demonstrated severe symmetrical brain atrophy especially in the frontal and temporal lobes, but not in the cerebellum. The areas of cortical hyperintensity on the initial FLAIR image disappeared and multiple high signal spots were observed in the white matter on the follow-up FLAIR image (*white arrows*). Hyperintense lesions were seen in the anterior putamen bilaterally on the T_1-weighted image (*white arrowhead*).

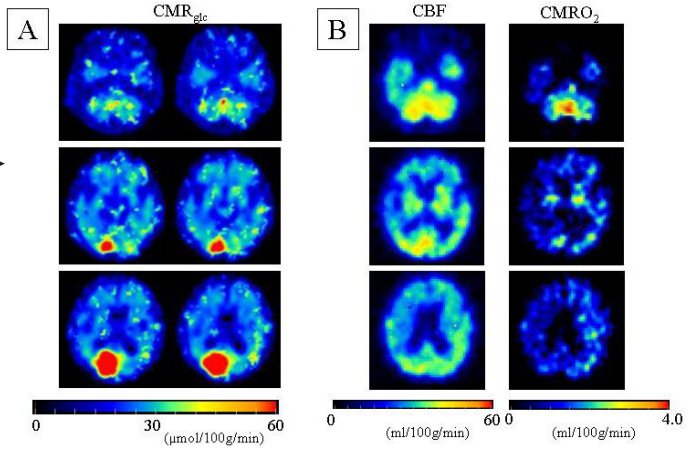


Fig. 4 The cerebral metabolic rate for glucose (CMR_{glc}) ▶ evaluation with FDG-PET on the 25th day after hypoglycemic coma (A). The cerebral blood flow (CBF) and cerebral metabolic rate for oxygen ($CMRO_2$) evaluations with PET on the 32nd day after hypoglycemic coma (B). (A) Severe glucose hypometabolism was observed in the whole brain except for the right parieto-occipital cortex which showed markedly increased glucose metabolism. (B) The CBF study showed diffuse hypoperfusion in the cerebrum and the oxygen metabolism was also suppressed in the whole brain.

Table 1 Regional CMR_{glc}, CBF and $CMRO_2$ on initial and follow-up PET examinations

	MRI abnormality	Initial PET			Follow-up PET		
		CMR_{glc}	CBF	$CMRO_2$	CMR_{glc}	CBF	$CMRO_2$
right							
frontal	+	72	51	2.6	28	29	1.0
parietal	+	72	52	3.0	103	30	1.6
temporal	+	47	55	2.3	26	29	1.2
occipital	+	77	54	2.8	30	31	1.5
thalamus	+	73	47	2.8	27	33	1.7
cerebellum	–	46	53	3.3	29	30	0.8
left							
frontal	–	44	43	2.6	28	41	1.8
parietal	–	43	49	2.7	26	35	1.3
temporal	–	41	49	2.9	30	43	2.0
occipital	+	49	48	1.6	30	36	2.0
thalamus	–	43	47	2.8	24	30	1.7
cerebellum	+	72	57	3.5	30	31	1.2
control cortex		44.3	45.6	2.9			

on the initial FLAIR image disappeared except for the insular cortex, and multiple high signal spots were observed in the white matter on the follow-up FLAIR image (Fig. 3A). Small hyperintense lesions were seen in the anterior putamen bilaterally on the T_1-weighted image (Fig. 3B). Follow-up FDG-PET examination was performed on the 25th hospital day and revealed severe glucose hypometabolism ($rCMR_{glc}$: 25–30 μmol/100 g/min) in the whole brain except for the right parieto-occipital cortex which showed markedly increased glucose metabolism ($rCMR_{glc}$: 103 μmol/100 g/min) (Fig. 4A). The blood flow and metabolism for oxygen in the brain were examined on the 32nd hospital day (Fig. 4B). The CBF study showed diffuse hypoperfusion and the regional CBF in the right cerebral cortex (rCBF: 29–31 m*l*/100 g/min) was lower compared with that in the left cerebral cortex (rCBF: 35–43 m*l*/100 g/min). The oxygen metabolism was also suppressed in the whole brain, and the regional $CMRO_2$ in the right cerebral cortex ($CMRO_2$: 1.0–1.6 m*l*/100 g/min) was lower compared with that in the left cerebral cortex ($CMRO_2$: 1.3–2.0 m*l*/100 g/min). The absolute values for $rCMR_{glc}$, rCBF and $rCMRO_2$ on the initial and follow-up PET examination are shown in Table 1. The patient remained comatose and was referred to an affiliated hospital on the 39th hospital day.

DISCUSSION

Acute hypoglycemia can impair neurological function as the brain is strictly dependent on glucose for oxidative metabolism. In treated diabetes mellitus, recurrent hypoglycemia may manifest as transient neurological deficits in adults[6] and more frequently in children.[2,3] These transient neurological deficits may be generalized such as confusion, restlessness and generalized seizures. At times, for unknown reasons, the neurological deficits are of a focal nature, including hemiplegia, focal sensory deficits and focal epileptic seizure. Only a few reports have discussed the association between the focal epileptic episodes and hypoglycemia.[7,8] Our patient had focal status epilepticus following severe hypoglycemia and the FDG-PET evaluation of the brain on the 4th hospital day demonstrated asymmetrical glucose hypermetabolism corresponding to the hyperintense areas on the FLAIR image. Transiently increased signal intensity in the cerebral cortex on the FLAIR image and diffusion-weighted image (DWI) has been reported recently in prolonged hypoglycemia.[9] However, the MRI abnormality observed in our patient is thought to be the result of focal status epilepticus not hypoglycemic brain injury for several reasons. First, symmetrical brain damage is usually demonstrated radiologically in the human brain after hypoglycemic brain injury.[5] Second, in addition to MRI signal changes in the region of the presumed cortical focus, we noted abnormality in structures anatomically remote from the focus; the ipsilateral thalamus and the contralateral cerebellum. Hyperintensity of these remote regions on the MRI has been described previously in patients with focal status epilepticus.[10] Third, the distribution of morphologic abnormalities largely matched the area of increased glucose metabolism on the FDG-PET study. We recently reported a similar case with focal status epilepticus in which the patient's glucose hypermetabolism was observed in the ipsilateral cerebral cortices, basal ganglia and contralateral cerebellar cortex.[11] Reversible MR change in the involved cortical gray matter on the FLAIR and T_2-weighted images was also demonstrated previously in patients with status epilepticus not related to hypoglycemic encephalopathy.[12,13] Kim et al. reported that the peri-ictal DWIs revealed increased signal inten-

sity in the area of the presumed cortical focus concomitant with reduced apparent diffusion coefficient reflecting seizure-related cytotoxic edema.[13] Our patient showed a profound glucose hypermetabolism with mild increase in the rCBF in the area of increased signal intensity on the FLAIR and T_2-weighted images. The acute consequence of seizures associated with status epilepticus is an increase in cellular glucose uptake and metabolism, resulting in increased CMR_{glc}. Hyperperfusion of the affected hemisphere during status epilepticus has been explained as an ictal phenomenon in response to elevated metabolic demand.[14] If the compensatory increase of the blood flow is not sufficient, anaerobic metabolism may take over, resulting in decrease of phosphocreatine and excess production of lactic acid. With status epilepticus, the metabolism is markedly increased, resulting in depletion of adenosine triphosphate and energy reserve at its later stage. Inevitably, this will result in impaired ion exchange pump functions and increased ion permeability of the cells, resulting in cytotoxic brain edema.[12] One of the interesting findings observed in our patient is the discrepancy between the glucose metabolism and blood flow in the region of the presumed cortical focus and remote areas. Also, oxygen metabolism was not increased in the area of accelerated glucose metabolism. Classically, during neuronal activation such as seizures, the cerebral perfusion and metabolism are closely coupled.[15] Uncoupling of local cerebral glucose utilization and local cerebral blood flow was previously reported in induced status epilepticus in rats.[16] Although we did not examine the FDG-PET study (day 4) and CBF-PET (day 5) on the same day, the patient was treated in a same fashion and the physiological status during the examination was not different between the two PET studies. The exact reason for the discrepancy between the glucose and oxygen metabolism on ictal PET images cannot be determined. Mitochondrial dysfunction has been recently reported in epileptic seizures.[17] The observed imbalance between the glucose utilization and oxygen consumption could suggest that an impairment of oxygen utilization by the mitochondria could occur in the epileptic focus during long lasting status epilepticus. Cytotoxic brain edema due to markedly increased anaerobic glucose metabolism without compensatory increase of the blood flow during long-lasting status epilepticus may account for the brain abnormality observed on the early MRI.

Follow-up MRI examined on the 33rd hospital day showed severe symmetrical brain atrophy and the patient showed persistent consciousness disturbance. Of course, we cannot simply compare the ictal and postictal MRI images because the patient had brain edema during status epilepticus. Severe hypoxia/ischemia and hypoglycemia are leading causes of subacute diffuse brain atrophy and irreversible neurologic sequelae. Although the hemodynamics and respiration in the patient were stable on admission, she might have had severe hypoxia due to status epilepticus before the hospitalization. It is practically difficult to distinguish between cerebral damage due to hypoxia/ischemia and hypoglycemia. A serial MRI study has shown symmetrical lesions in the basal ganglia, thalamus, and/or substantia nigra with minor hemorrhage in patients with hypoxic/ischemic encephalopathy but not of hypoglycemic encephalopathy.[5,18] Our patient had a small hyperintense lesion on the T_1-weighted MR image in the anterior putamen bilaterally and the lesion is compatible to the MRI finding in subacute hemorrhage. Hypoglycemic diffuse brain damage can be also distinguished from hypoxic/ischemic encephalopathy in that the cerebellum and the thalamus are usually involved.[18,19] Our patient showed severe symmetrical brain atrophy especially in the frontal and temporal lobes, but not in the cerebellum on the follow-up MRI. The MRI findings suggest that hypoglycemic encephalopathy is mainly responsible for the delayed diffuse brain atrophy in this patient and hypoxic/ischemic encephalopathy is partially responsible for the delayed lesion in the basal ganglia.

CONCLUSION

Our case reveals that prolonged seizure activity produces profound glucose hypermetabolism and mild hyperemia in the region of the presumed cortical focus of epilepsy and in structures anatomically remote from the focus. One of the mechanisms of transient abnormality on the MRI during focal status epilepticus is cytotoxic brain edema in the cortex due to energy failure. The MRI findings suggest that hypoglycemic encephalopathy is mainly responsible for the delayed diffuse brain atrophy in this patient. Simultaneous examination of the cerebral blood flow and metabolism using PET can provide useful information about the pathology in patients with status epilepticus.

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